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(30)Priority

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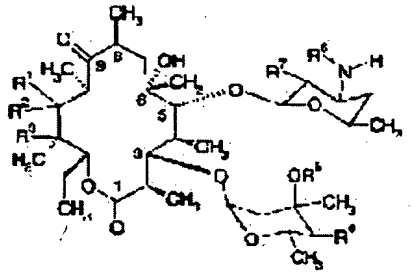
## (54) PRODUCTION OF ERYTHROMYCIN DERIVATIVE

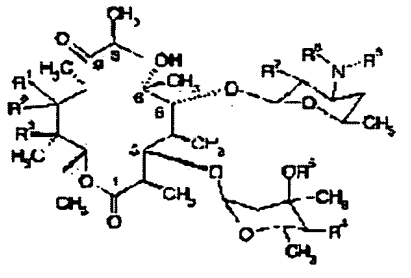
(57)Abstract:

PROBLEM TO BE SOLVED: To produce the subject high-purity compound useful as a preventing agent or a therapeutic agent for digestive diseases in high yield in a short time by carrying out an N-alkylating, an N-alkenylating or an N-alkynylating reaction of an N-demethylerythromycin derivative in the presence of a specific reactional solvent.



I

SOLUTION: A compound represented by formula I (either one of R1 and R2 is H and the other is hydroxyl group or R1 and R2 are mutually bonded to denote O; R3 is H or hydroxyl group which may be substituted; R4 and R7 are each H or hydroxyl group; R5 is H or a lower alkyl; and R6 is a 1-6C alkyl, a 2-6C alkenyl or the like) or its salt is reacted with a compound represented by the formula R8-X (R8 is R6; and X is a leaving group) in the presence of cyclic amides or in the coexistence of the cyclic amides and alkylnitriles to produce the objective compound represented by formula II. The reaction is preferably carried out in the coexistence of N-



II

methyl-2- pyrrolidone which is the cyclic amides and acetonitrile that is the alkylnitriles.

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LEGAL STATUS

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* NOTICES *



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CLAIMS

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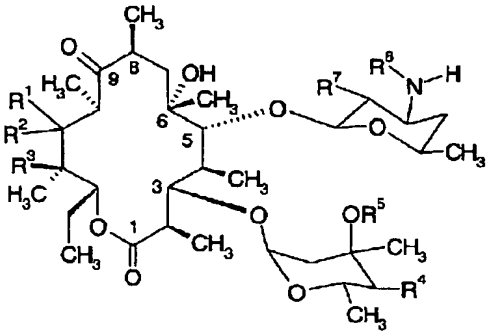
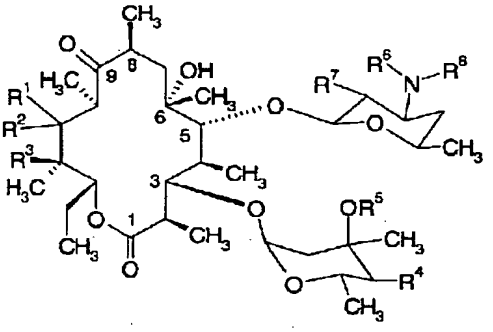
[Claim(s)]

[Claim 1] Formula [** 1]



(I)

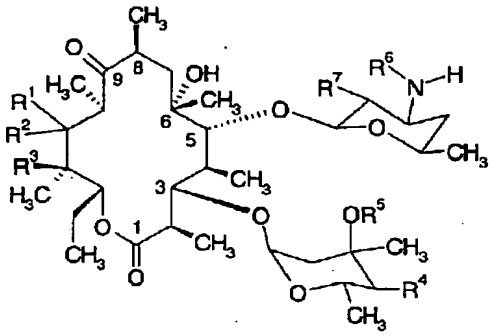
One side among [type R1 and R2 [ whether the hydroxyl group with which another side may be permuted from hydrogen is shown, and ] R1 and R2 join together mutually. O= It is shown and R3 shows hydrogen or the hydroxyl group which may be permuted. R4 shows hydrogen or a hydroxyl group, and R5 shows hydrogen or a low-grade alkyl group. R6 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6. R7 the compound expressed with] which shows hydrogen or a hydroxyl group, or its salt under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril Formula It is the formula [** 2] characterized by making it react with the compound expressed with R8-X [R8 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6 among a formula, and X shows a leaving group], or its salt.



(II)

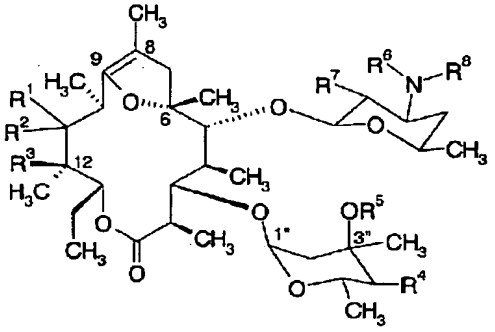
It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt.

[Claim 2] Formula [** 3]



(I)

One side among [type R1 and R2 [ whether the hydroxyl group with which another side may be permuted from hydrogen is shown, and ] R1 and R2 join together mutually. O= It is shown and R3 shows hydrogen or the hydroxyl group which may be permuted. R4 shows hydrogen or a hydroxyl group, and R5 shows hydrogen or a low-grade alkyl group. R6 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6. R7 the compound expressed with] which shows hydrogen or a hydroxyl group, or its salt under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril Formula It is the formula [** 4] characterized by processing from an acid after making it react with the compound expressed with R8-X [R8 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6 among a formula, and X shows a leaving group], or its salt.



(III)

It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt.

[Claim 3] either R1 or R2 -- hydrogen -- another side -- a hydroxyl group and the manufacturing method according to claim 2 a hydroxyl group and whose R8 a methyl group and R7 are [ R3 / a hydroxyl group and R4 / a hydroxyl group and R5 ] isopropyl groups for a methyl group and R6.

[Claim 4] The manufacturing method according to claim 2 whose cyclic amide is N-methyl-2-pyrrolidones.

[Claim 5] The manufacturing method according to claim 2 whose alkyl nitril is acetonitriles.

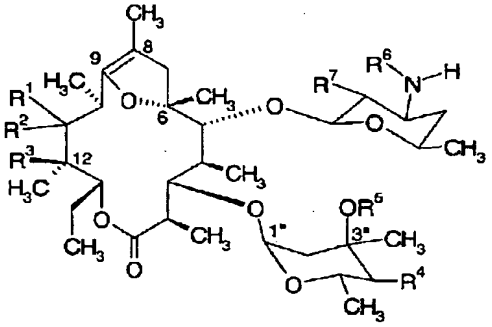
[Claim 6] The inside of a formula (I) [type and each notation are a manufacturing method

according to claim 2 to which the compound expressed with] which shows claim 2 publication and this meaning, or its salt is made to react under coexistence with cyclic amide and alkyl nitril with the compound expressed with formula R8-X [each notation shows claim 2 publication and this meaning among a formula].

[Claim 7] The manufacturing method according to claim 6 whose quantitative ratios of cyclic amide and alkyl nitril are 1:0.1 thru/or 1:10.

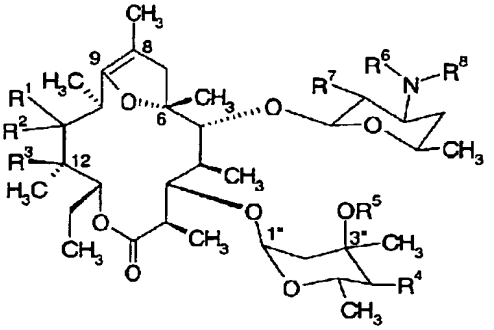
[Claim 8] the amount of the mixed liquor used of cyclic amide and alkyl nitril -- a formula -- the compound expressed with (I [each notation shows claim 2 publication and this meaning among a formula]), or its salt Manufacturing method according to claim 6 which are 0.5 thru/or the amount (v/w) of 50 times to 1.

[Claim 9] Formula [** 5]



(IV)

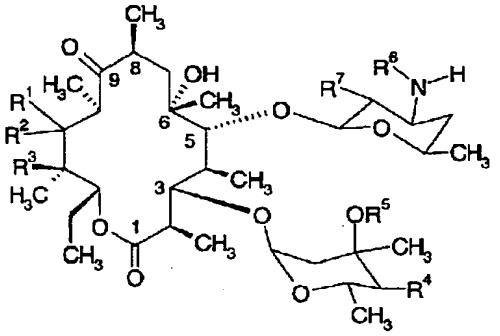
One side among [type R1 and R2 [ whether the hydroxyl group with which another side may be permuted from hydrogen is shown, and ] R1 and R2 join together mutually. O= It is shown and R3 shows hydrogen or the hydroxyl group which may be permuted. R4 shows hydrogen or a hydroxyl group, and R5 shows hydrogen or a low-grade alkyl group. R6 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6. R7 the compound expressed with] which shows hydrogen or a hydroxyl group, or its salt under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril Formula It is the formula [** 6] characterized by making it react with the compound expressed with R8-X [R8 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6 among a formula, and X shows a leaving group], or its salt.



(III)

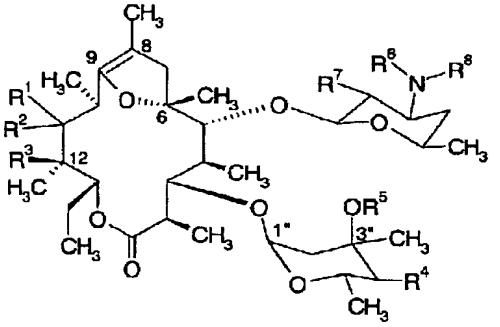
It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt.

[Claim 10] Formula [** 7]



(I)

One side among [type R1 and R2 [ whether the hydroxyl group with which another side may be permuted from hydrogen is shown, and ] R1 and R2 join together mutually. O= It is shown and R3 shows hydrogen or the hydroxyl group which may be permuted. R4 shows hydrogen or a hydroxyl group, and R5 shows hydrogen or a low-grade alkyl group. R6 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6. After R7 processes from an acid the compound expressed with] which shows hydrogen or a hydroxyl group, or its salt, under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril Formula It is the formula [** 8] characterized by making it react with the compound expressed with R8-X [R8 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6 among a formula, and X shows a leaving group], or its salt.



(III)

It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt.

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DETAILED DESCRIPTION

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[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the manufacturing method of an erythromycin derivative useful as physic for prevention of constipation by the digestive system disease of mammalian especially human postoperative intestinal obstruction, the diabetic gastroparalysis, dyspepsia, esophagitis regurgitica, pseudoileus, the digestive organ symptoms (epigastric region feeling of fullness, an epigastric region oppressive feeling, nausea, vomiting, heartburn, anorexia, epigastralgia, epigastrium tenderness, etc.) accompanying the postgastrectomy syndrome, chronic gastritis, irritable colon syndrome, morphine, and anticancer agent administration etc., or a therapy, or its salt.
[0002]
[Description of the Prior Art] As a compound which has alimentary canal contraction movement promotion activity, the N-DEMECHIRU-N-isopropyl -8 which is an erythromycin derivative, 9-anhydro erythromycin A-6, 9-hemiacetal and N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal are indicated by JP,10-067795,A. The method of manufacturing the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal is indicated by making N-DEMECHIRU erythromycin A react with an isopropyl-ized agent, and processing it from an acid continuously under existence of a base, in this official report. Moreover, the method of manufacturing N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal is indicated by processing N-DEMECHIRU erythromycin A from an acid, making 6 and 9-hemiacetal ring form, and making it react to the bottom of existence of a base with an ethylation agent the back.
[0003]
[Problem(s) to be Solved by the Invention] When N-alkylation reaction was performed to above-mentioned JP,10-067795,A under organic base existence in the reaction solvent of a publication by using N-DEMECHIRU erythromycin A as a raw material compound, there was a

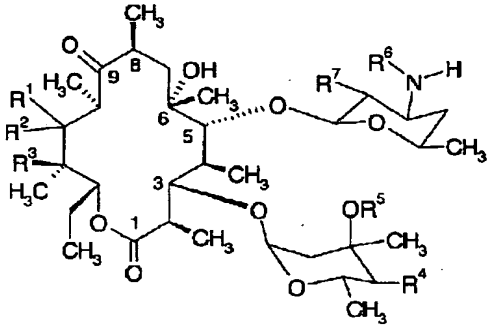
problem of the crystal of a raw material compound tending to deposit during a reaction, and requiring long duration for completing a reaction since it is a heterogeneous reaction. On the other hand, although the deposit of a raw material crystal was avoided and reaction time was shortened under inorganic base existence when the above-mentioned N-alkylation reaction was performed, there was a problem that actuation of separating the product made into the purpose from the base after reacting was complicated. Moreover, when N-alkylation reaction was performed to above-mentioned JP,10-067795,A under base existence in the reaction solvent of a publication after processing from an acid by using N-DEMECHIRU erythromycin A as a raw material compound, there was a problem that reaction selectivity became low.

[0004]

[Means for Solving the Problem] The result to which this invention persons examined many things wholeheartedly about manufacture of an erythromycin derivative, The soluble high solvent of N-DEMECHIRU erythromycin derivatives (for example, N-DEMECHIRU erythromycin A etc.), For example, cyclic amide (an example, a N-methyl-2-pyrrolidone, N-methyl-2-piperidone, etc.) or these cyclic amide and alkyl nitril (an example and an acetonitrile --) By using a mixed solvent with propionitrile, butyronitrile, etc. as a reaction solvent, and giving N-alkylation, the formation of N-alkenyl, or N-alkynyl-ized reaction That it can avoid that a raw material deposits and reaction time can be sharply shortened in the system of reaction, and by processing from an acid further 8, 9-anhydro erythromycin -6 which are represented by the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal and N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal, It found out that 9-hemiacetal derivative could be obtained with sufficient yield. Moreover, after this invention persons process from an acid N-DEMECHIRU erythromycin derivative represented by N-DEMECHIRU erythromycin A, Cyclic amide (an example, a N-methyl-2-pyrrolidone, N-methyl-2-piperidone, etc.) or these cyclic amide and alkyl nitril (an example and an acetonitrile --) By using a mixed solvent with propionitrile, butyronitrile, etc. as a reaction solvent, and giving N-alkylation, the formation of N-alkenyl, or N-alkynyl-ized reaction Reaction selectivity improves and compaction of reaction time also becomes possible. 8, 9-anhydro erythromycin -6 which are represented by the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal and N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal, It found out that 9-hemiacetal derivative could be obtained with sufficient yield. This invention was completed as a result of this invention persons' inquiring further wholeheartedly based on these knowledge.

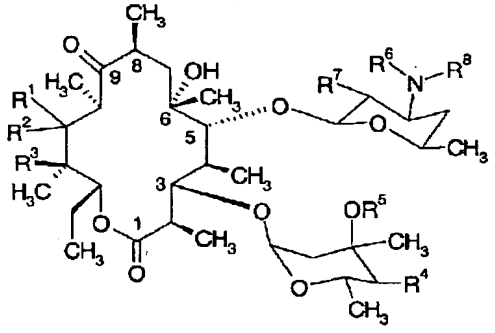
[0005] This invention offers the manufacturing method which manufactures an erythromycin derivative especially the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal and N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal in high quality (high grade) and high yield, and a short time.

[0006] That is, this invention is [1] type [** 9].



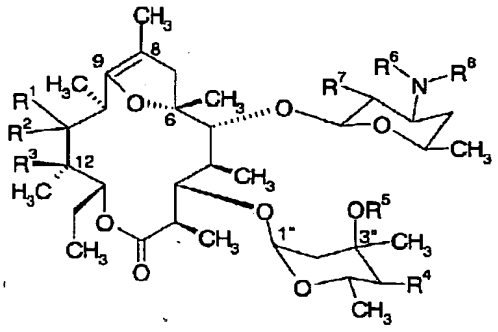
(I)

One side among [type R1 and R2 [ whether the hydroxyl group with which another side may be permuted from hydrogen is shown, and ] R1 and R2 join together mutually. O= It is shown and R3 shows hydrogen or the hydroxyl group which may be permuted. R4 shows hydrogen or a hydroxyl group, and R5 shows hydrogen or a low-grade alkyl group. R6 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6. R7 is formula R8-X under existence of cyclic amide [ salt / its / the compound expressed with] which shows hydrogen or a hydroxyl group, or / [it is hereafter written as a compound (I)] ], or coexistence with cyclic amide and alkyl nitril. (V)
It is the formula [** 10] characterized by making it react with the compound expressed with [R8 shows the alkyl group of carbon numbers 1-6, the alkenyl radical of carbon numbers 2-6, or the alkynyl group of carbon numbers 2-6 among a formula, and X shows a leaving group], or its salt [for it to be hereafter written as a compound (V)].



(II)

It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt [it is hereafter written as a compound (II)].;
[2] The formula characterized by processing it from an acid after making a compound (I) react with a compound (V) under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril [** 11]



(III)

It is the manufacturing method of the compound expressed with [each notation shows the above and this meaning among a formula], or its salt [it is hereafter written as a compound (III)].;

[3] Manufacturing method of the aforementioned [2] publication [ either R1 or R2 ] of another side from hydrogen a hydroxyl group and whose R8 a methyl group and R7 are [ a hydroxyl group and R3 / a hydroxyl group and R4 / a hydroxyl group and R5 ] isopropyl groups for a methyl group and R6;

[4] Manufacturing method of the aforementioned [2] publication whose cyclic amide is N-methyl-2-pyrrolidones;

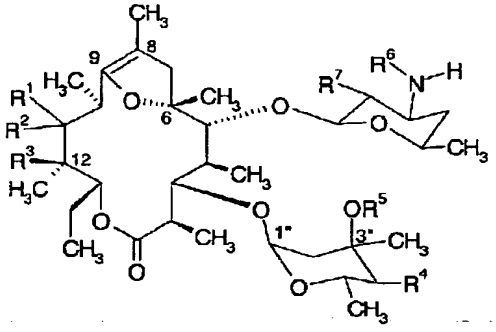
[5] Manufacturing method of the aforementioned [2] publication whose alkyl nitril is acetonitriles;

[6] Manufacturing method of the aforementioned [2] publication to which a compound (I) is made to react with a compound (V) under coexistence with cyclic amide and alkyl nitril;

[7] Manufacturing method of the aforementioned [6] publication whose quantitative ratios of cyclic amide and alkyl nitril are 1:0.1 thru/or 1:10;

[8] Manufacturing method of the aforementioned [6] publication whose amount of the mixed liquor used of cyclic amide and alkyl nitril is 0.5 thru/or the amount (v/w) of 50 times to a compound (I) 1;

[9] Formula [** 12]



(IV)

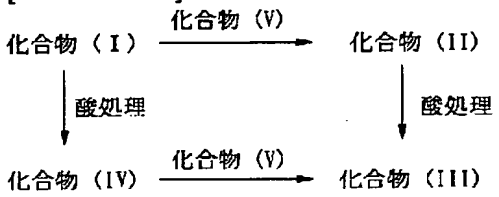
It is the manufacturing method of the compound (III) characterized by making it react [ salt / its / the compound expressed with [each notation shows the above and this meaning among a

formula], or / [it is hereafter written as a compound (IV)] ] with a compound (V) under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril.;

[10] After processing a compound (I) from an acid, it is related with the manufacturing method of the compound (III) characterized by making it react with a compound (V) under existence of cyclic amide or coexistence with cyclic amide and alkyl nitril etc.

[0007] The outline of the process of this invention is shown below.

[Formula 13]




[0008] Among the above-mentioned formula, one side shows the hydroxyl group with which another side may be permuted from hydrogen, or R1 and R2 combine R1 and R2 mutually. O= It is shown. The hydroxyl group which may be permuted by the this hydroxyl group which may be permuted by one to C6 alkyls (an example, methyl, ethyl, propyl, isopropyl, hexyl, etc.), two to C6 alkenyl (an example, vinyl, 1-propenyl, an allyl compound, hexenyl, etc.), or two to C6 alkynyl (an example, ethynyl, 1-propynyl, 2-propynyl, hexynil, etc.) is mentioned. R1 and R2 are desirable, and one side is [ another side ] a hydroxyl group from hydrogen. R3 shows hydrogen or the hydroxyl group which may be permuted. The same thing as the above is mentioned as a this hydroxyl group which may be permuted. R3 is a hydroxyl group preferably to the hydroxyl group and pan which were preferably permuted by the hydroxyl group or one to C4 alkyl. R4 shows hydrogen or a hydroxyl group. It is a hydroxyl group preferably. R5 shows hydrogen or a low-grade alkyl group. It is a methyl group preferably [ it is desirable and ] to C1-6 alkyl group and a pan. R6 shows C1-6 alkyl groups (an example, methyl, ethyl, propyl, isopropyl, hexyl, etc.), C2-6 alkenyl radicals (an example, vinyl, 1-propenyl, an allyl compound, hexenyl, etc.), or C1-6 alkynyl groups (an example, ethynyl, 1-propynyl, 2-propynyl, hexynil, etc.). It is a methyl group preferably [ it is desirable and ] to C1-4 alkyl group and a pan. R7 shows hydrogen or a hydroxyl group. It is a hydroxyl group preferably. R8 shows C1-6 alkyl groups (an example, methyl, ethyl, propyl, isopropyl, hexyl, etc.), C2-6 alkenyl radicals (an example, vinyl, 1-propenyl, an allyl compound, hexenyl, etc.), or C2-6 alkynyl groups (an example, ethynyl, 1-propynyl, 2-propynyl, hexynil, etc.). An ethyl group or an isopropyl group is shown preferably [ it is desirable and ] in C1-4 alkyl group and a pan. It is an isopropyl group most preferably. X shows a leaving group, for example, halogens (an example, chloro, BUROMO, iodine, etc.), a C1-3 alkyl sulfonyl (an example, methane sulfonyl), a PARATORU en sulfonyl, etc. are mentioned. It is a halogen preferably.

[0009] As a compound (I), an N-DEMECHIRU erythromycin A derivative (it indicates to JP,47-

9129,A), an N-DEMECHIRU erythromycin B derivative, an N-DEMECHIRU erythromycin C derivative, an N-DEMECHIRU erythromycin D derivative (hereafter, these may be named generically and N-DEMECHIRU erythromycin derivative may be called), etc. are specifically mentioned. A compound (I) can be manufactured according to the approach of applying to the below-mentioned example 1 of reference at the approach of a publication, or it by using erythromycin derivatives (for example, erythromycin A etc.) as a raw material compound. Erythromycin A, Erythromycin B, Erythromycin C, and Erythromycin D are well-known compounds, and can also come to hand as a commercial item ([Erythromycins C and erythromycin D:Abbott (U.S.)], such as erythromycin A:BIOCHEMIE (Austria) and Upjohn (U.S.), and erythromycin B:Proter (Italy), etc.).

[0010] As a compound (III), for example 8, 9-anhydro erythromycin A-6, 9-hemiacetal derivative, 8, 9-anhydro erythromycin B-6, 9-hemiacetal derivative, 8, 9-anhydro erythromycin C-6, 9-hemiacetal derivative, 8, 9-anhydro erythromycin D-6, 9-hemiacetal derivative (hereafter, these may be named generically and 8, 9-anhydro erythromycin -6, and 9-hemiacetal derivative may be called), etc. are mentioned. Specifically The N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, The 12-dehydroxy-4"-dehydroxy-N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, The N-DEMECHIRU-N-isopropyl-12-methoxy -8, 9-anhydro erythromycin A-6, 9-hemiacetal, And N-DEMECHIRU-N-isopropyl-12-methoxy-11-oxo-- 8, 9-anhydro erythromycin A-6, 9-hemiacetal, etc. are mentioned. more -- desirable -- The N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, etc. are mentioned. Either R1 or R2 is [ another side ] a hydroxyl group and the compound (the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal) a hydroxyl group and whose R8 a methyl group and R7 are [ R3 / a hydroxyl group and R4 / a hydroxyl group and R5 ] isopropyl groups for a methyl group and R6 from hydrogen most preferably.

[0011] As a desirable example of a compound (V), halogenation C1-6 alkyl, halogenation C2-6 alkenyl, halogenation C2-6 alkynyl, etc. are mentioned. They are halogenation isopropyl and halogenation ethyl still more preferably. As this halogen, chloro, BUROMO, iodine, and division iodine are desirable. A methyl iodide, an ethyl iodide, propyl iodide, iodation isopropyl, iodation propenyl, iodation ethynyl, iodation propynyl, etc. are mentioned, and, specifically, a methyl iodide, an ethyl iodide, propyl iodide, and iodation isopropyl are especially desirable. Iodation isopropyl (2-iodine propane) is the most desirable.

[0012] A compound (II) can use a compound (I) as a reaction solvent for the mixed liquor of cyclic amide or these cyclic amide, and alkyl nitril etc., and can manufacture it by making it react with a compound (V). the amount of the compound (V) used -- (Compound I) [N-DEMECHIRU erythromycin derivative (or the bis-object)] 1 mol -- receiving -- about 1 - the

100-mol equivalent -- it is about 1 - the 25-mol equivalent preferably, and they are especially about 2 - the 15-mol equivalent. This reaction is performed under the independent solvent of cyclic amide (an example, a N-methyl-2-pyrrolidone, N-methyl-2-piperidone, etc.), or the mixed solvents (an example, an acetonitrile, propionitrile, butyronitrile, etc.) of cyclic amide (an example, a N-methyl-2-pyrrolidone, N-methyl-2-piperidone, etc.) and alkyl nitril. Furthermore, a kind of halogenated hydrocarbon (an example, chloroform, dichloromethane, etc.), ether, ketones (an example, ethyl ether, tetrahydrofuran, etc.), ester (an example, an acetone, methyl ethyl ketone, etc.), alcohols (an example, ethyl acetate, etc.), alkyl (example, methanol, ethanol, etc.) nitril, and amides, such as example, N.N-dimethylformamide, N, and N-dimethyl amide and cyclic amide, or two sorts or more of mixed solvents may be used. Especially, the mixed solvent of cyclic amide and C1-5 alkyl nitril is desirable. It is a N-methyl-2-pyrrolidone preferably as cyclic amide. It is an acetonitrile preferably as C1-5 alkyl nitril.

[0013] the case where the independent solvent of cyclic amide is used -- the amount of the cyclic amide used -- a compound (I) 1 -- receiving -- about 0.5 thru/or the amount (v/w) of 50 times -- they are about 1 thru/or the amount (v/w) of 50 times preferably. the case where the mixed liquor of cyclic amide and alkyl nitril is used -- the amount of this mixed liquor used -- a compound (I) 1 -- receiving -- 0.5 thru/or the amount (v/w) of 50 times -- they are about 1 thru/or the amount (v/w) of 50 times preferably. the quantitative ratio of cyclic amide and alkyl nitril -- usually -- about 1:0.1 thru/or about 1:10 (v:v) -- desirable -- about 1:0.1- it is about 1:5 (v:v). This reaction is usually performed to the bottom of existence of a base. As this base, the third class amine and a metal carbonate are mentioned preferably, and the third class amines (an example, triethylamine, tree n propylamine, etc.), metal carbonates (an example, potassium carbonate, a sodium carbonate, lithium carbonate, etc.), metal hydrogencarbonates (a sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), etc. are especially suitable for a sodium carbonate and triethylamine. the amount of the base used in this reaction -- (Compound I) [N-DEMECHIRU erythromycin derivative (or the bis-object)] 1 mol -- receiving -- about 1 - the 100-mol equivalent -- desirable -- about 1 - the 30-mol equivalent -- they are about 1 - the ten-mol equivalent still more preferably. The case where the mixed solvent of a N-methyl-2-pyrrolidone and an acetonitrile is used can be mentioned, and a desirable example can shorten reaction time sharply, and can obtain the purpose compound with sufficient yield.

[0014] for example, the case where the mixed solvent of a N-methyl-2-pyrrolidone and an acetonitrile is used in this reaction -- the mixing ratio -- about 1:0.1- about 1:10 (v:v) -- desirable -- about 1:0.1- it is about 1:5 (v:v). this reaction -- the boiling point (about 100 degrees C) of the bottom of ice-cooling (about 0 degree C) - a solvent -- desirable -- room temperature (about 15-25 degrees C) - about 90 degrees C of compaction of reaction time are possible by especially carrying out at about 60-80 degrees C. The reaction time of this reaction is about 1 - 8 hours more preferably for about 1 to 10 hours for about 1 to 30 hours. The

obtained compound (II) may be given to the next reaction, without isolating.
[0015] A compound (III) can be manufactured by processing a compound (II) from an acid. As an acid in processing with an acid, for example, organic acids (a formic acid, an acetic acid, a propionic acid, oxalic acid, boletic acid, maleic acid, etc.) or mineral acids (a sulfuric acid, phosphoric acid, etc.) are mentioned, and an acetic acid is especially desirable. These acids can also be used diluting them with halogenated hydrocarbon, ether, ester, and ketones suitably. the amount of this acid used -- compound (II)1 mol -- receiving -- about 1 - the 200-mol equivalent -- desirable -- about 30 - the 100-mol equivalent -- they are about 40 - the 70-mol equivalent especially preferably. this processing reaction -- the boiling point (about 100 degrees C) of the bottom of ice-cooling (about 0 degree C) - a solvent -- desirable -- bottom of ice-cooling (about 0 degree C) - 80 degrees C is especially performed at room temperature (about 15-25 degrees C) -50 degree C. The reaction time in this processing reaction is about 1 - 5 hours preferably for about 1 to 10 hours.
[0016] A compound (IV) can be manufactured by processing a compound (I) from an acid. The reaction condition is the same as that of the reaction which obtains a compound (III) than a compound (II). The obtained compound (IV) may be given to the next reaction, without isolating. A compound (III) can use a compound (IV) as a reaction solvent for the mixed liquor of cyclic amide (an example, a N-methyl-2-pyrrolidone, N-methyl-2-piperidone, etc.) or these cyclic amide, and alkyl nitril (an example, an acetonitrile, propionitrile, butyronitrile, etc.) etc., and can manufacture it by making it react with a compound (V). The reaction condition is the same as that of the reaction which obtains a compound (I) from a compound (II).
[0017] the compound (III) (for example, the N-DEMECHIRU-N-alkyl -8, 9-anhydro erythromycin -6, and 9-hemiacetal derivative --) obtained in this way The N-DEMECHIRU-N-alkenyl -8, 9-anhydro erythromycin -6, 9-hemiacetal derivative or N-DEMECHIRU-N-alkynyl -8, 9-anhydro erythromycin -6, 9-hemiacetal derivative, etc. the very thing -- a well-known means, for example, concentration, acidity-or-alkalinity conversion, ****, and solvent extraction -- it crystallizes, and it can crystallize and can refine with recrystallization and a chromatography method further after isolation. After making the rough crystal of this compound recrystallize as isopropanol solvate out of water isopropanol, i.e., isopropanol, / water mixed solvent, by making it recrystallize from an acetonitrile / water mixed solvent, yield is good and the purpose compound can especially be substantially obtained as a pure crystal. the isopropanol used for recrystallization -- a substrate -- receiving -- about 1 - about 20 time capacity -- capacity uses about two to 5 times preferably -- having -- water -- a substrate -- receiving -- about one to 20 time capacity -- capacity is used about two to 10 times preferably. the ratio of isopropanol and water -- about 1:0.5- about 1:3 (v:v) -- desirable -- about 1:1- it is about 1:2 (v:v).
[0018] Moreover, the compound used in this invention manufacturing method or the compound obtained may form a salt by processing from an acid. As this acid, organic acids (an example,

the Glico peptone acid, stearin acid, a propionic acid, a RAKUTOPION acid, oxalic acid, a maleic acid, boletic acid, a succinic acid, a lactic acid, trifluoroacetic acid, an acetic acid, methansulfonic acid, Para toluenesulfonic acid, benzenesulfonic acid, etc.), mineral acids (an example, a sulfuric acid, a hydrochloric acid, a hydroiodic acid, a phosphoric acid, nitric acid, etc.), etc. are mentioned, for example. As a salt of the compound used by this invention, or the compound obtained, the salt permitted pharmacologically is desirable, for example, a salt with a salt with an inorganic acid, a salt with an organic acid, basicity, or acidic amino acid etc. is mentioned. As a suitable example of a salt with an inorganic acid, a salt with a hydrochloric acid, a hydrobromic acid, a nitric acid, a sulfuric acid, a phosphoric acid, etc. is mentioned, for example. As a suitable example of a salt with an organic acid, a salt with a formic acid, an acetic acid, trifluoroacetic acid, boletic acid, oxalic acid, a tartaric acid, a maleic acid, a citric acid, a succinic acid, a malic acid, methansulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. is mentioned, for example. As a suitable example of a salt with a basic amino acid, a salt with an arginine, a lysine, an ornithine, etc. is mentioned, for example, and a salt with an aspartic acid, glutamic acid, etc. is mentioned as a suitable example of a salt with acidic amino acid, for example.

[0019] On the compound and concrete target which are obtained by this invention, for example erythromycin derivatives, such as the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal and N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal, -- toxicity -- low -- mammalian (an example --) Digestive system diseases, such as Homo sapiens, a horse, a cow, Buta, a dog, a cat, a mouse, and a rat, Especially Human postoperative intestinal obstruction, the diabetic gastroparalysis, dyspepsia, esophagitis regurgitica, the digestive organ symptom (epigastric region feeling of fullness and an epigastric region oppressive feeling --) accompanying pseudoileus and the postgastrectomy syndrome It can use as physic for prevention of chronic gastritis, such as nausea, vomiting, heartburn, anorexia, epigastralgia, and epigastrium tenderness, irritable colon syndrome, morphine, constipation by anticancer agent administration, etc., or a therapy.

[0020]

[Embodiment of the Invention] Although an example and the example of reference are shown and this invention is explained still more concretely hereafter, this invention is not limited to these.

[0021]

[Example] It is a methanol about manufacture erythromycin A(BIOCHEMIE; Austria)10kg of 1N-DEMECHIRU erythromycin A of examples of reference. It dissolves in 56L and is sodium acetate and 3 hydrate. It is water about 9.4kg. The solution which dissolved in 16L was added and the temperature up was carried out to 50 degrees C. It is iodine, adding 1N NaOH suitably and holding pH of reaction mixture to 8.5. It is a methanol about 4.3kg. It was dropped holding

the liquid which dissolved in 40L at 50 degrees C over about 2 hours. The stirring reaction was carried out at 50 more degrees C for 2 hours. A reactant is cooled and it is 1-N sodium-thiosulfate solution. Addition decolorization of the 0.3L was carried out, reduced pressure distilling off of the solvent was carried out, and all volume was adjusted to about 110 L. Aqueous ammonia adjusts to pH10.5 25%, and it is water. 33L is dropped, it was made to crystalize and N-DEMECHIRU erythromycin A was obtained. It is a methanol about this compound. The heating dissolution is carried out at 20L, and they are after cooling and water to a room temperature. Add 33L, and it is made to crystalize and is the white crystal of N-DEMECHIRU erythromycin A. 7.9kg (81% of yield) was obtained.

[0022] After dissolving manufacture erythromycin A(BIOCHEMIE; Austria)10.3kg of 2N-DEMECHIRU erythromycin A of examples of reference in methanol 63L, it heated at 50 degrees C, and the water solutions 17L and 2 of 10.4kg of sodium acetate trihydrate and methanol solution 2'-azobis (2, 4-dimethyl-4-methoxy valeronitrile) [V-70(trade name); Wako Pure Chem] 46.3g 9.6L were added. 1N Methanol solution of 3.8kg of iodine 34L was dropped over 2 hours, having added the NaOH water solution suitably and holding pH of reaction mixture to 8.5. After stirring for 30 minutes, holding pH8.5 at 50 degrees C, 1-N sodium-thiosulfate water-solution 0.4L was added. After carrying out vacuum concentration until reaction mixture became the amount of abbreviation one half, aqueous ammonia adjusted to pH10.5 25%, and subsequently add water 36L, it was made to crystalize, and 8.8kg (87% of yield) of white crystals of N-DEMECHIRU erythromycin A was obtained.

[0023] It is 2-iodine propane to N-DEMECHIRU erythromycin A 24.0g obtained in the example 1 of manufacture reference of the 1N-DEMECHIRU-N-isopropyl -8 of examples, 9-anhydro erythromycin A-6, and 9-hemiacetal. 28.3g, triethylamine 8.4g and N-methyl-2-pyrrolidone 60ml is added, and it stirred for 4 hours and was made to react at 70 degrees C. It is ethyl acetate to reaction mixture. 190ml, water It is ethyl acetate about the water layer after adding 120ml, adjusting to pH8.5 by NaOH 5% and separating liquids. It extracted secondarily by 100ml. An ethyl acetate layer is doubled and it is water. It washed twice by 60ml, the solvent was condensed to 100ml under reduced pressure, and the N-DEMECHIRU-N-isopropyl-erythromycin A was obtained. It is an acetic acid to this N-DEMECHIRU-N-isopropyl-erythromycin A. 96ml is added, and it stirred for 3 hours and was made to react at a room temperature. It is ethyl acetate to a reactant. It cools after adding 70ml, after adjusting to pH8.5 by NaOH 20%, liquids are separated, and it is water to an ethyl acetate layer. 60ml was added and washed. The solvent was distilled off under reduced pressure of an ethyl acetate layer. It is an acetonitrile to the obtained residue. It is water, after adding 70ml, dissolving under heating and cooling to a room temperature. In addition, 70ml is crystallized and it is N-DEMECHIRU-N-isopropyl. - White crystal of 8, 9-anhydro erythromycin A-6, and 9-hemiacetal 20.1g (81% of yield) was obtained.

[0024] They are 2-iodine propane 5.6kg and triethylamine to N-DEMECHIRU erythromycin A 4.8kg obtained in the example 1 of manufacture reference of the 2N-DEMECHIRU-N-isopropyl -8 of examples, 9-anhydro erythromycin A-6, and 9-hemiacetal. 1.7kg and acetonitrile 6.0L, N-methyl-2-pyrrolidone 6.0L is added, and it stirred for 7 hours and was made to react at 70 degrees C. They are ethyl-acetate 38L and water to reaction mixture. It is ethyl acetate about the water layer after adding 24L, adjusting to pH8.5 by NaOH 5% and separating liquids. It extracted secondarily by 19L. An ethyl acetate layer is doubled and it is water. It washed twice by 12L, the solvent was condensed to 19L under reduced pressure, and the N-DEMECHIRU-N-isopropyl-erythromycin A was obtained. It is an acetic acid to this N-DEMECHIRU-N-isopropyl-erythromycin A. 19L is added, and it stirred for 3 hours and was made to react at a room temperature. Ethyl-acetate 14L is cooled after addition to a reactant, after adjusting to pH8.0 by NaOH 20%, liquids are separated, and it is water to an ethyl acetate layer. 12L was added and washed. The solvent was distilled off under reduced pressure of an ethyl acetate layer. It is an acetonitrile to the obtained residue. It is water, after adding 13L, dissolving under heating and cooling to a room temperature. It is made to crystalize 13L In addition, and is N-DEMECHIRU-N-isopropyl. - White crystal of 8, 9-anhydro erythromycin A-6, and 9-hemiacetal 4.3kg (85% of yield) was obtained.

[0025] They are 2-iodine propane 118.0g and triethylamine to N-DEMECHIRU erythromycin A 100.0g obtained in the example 1 of manufacture reference of the 1N-DEMECHIRU-N-isopropyl -8 of examples of a comparison, 9-anhydro erythromycin A-6, and 9-hemiacetal. 35.0g and acetonitrile 250ml is added, and it stirred for 24 hours and was made to react at 60-65 degrees C. It is ethyl acetate to reaction mixture. 800ml, water It is ethyl acetate about the water layer after adding 500ml, adjusting to pH8.5 by NaOH 5% and separating liquids. It extracted secondarily by 500ml. An ethyl acetate layer is doubled and it is water. It washed twice by 250ml, the solvent was condensed to 400ml under reduced pressure, and the N-DEMECHIRU-N-isopropyl-erythromycin A was obtained. 500ml of acetic acids is added to this N-DEMECHIRU-N-isopropyl-erythromycin A, and it stirred for 4 hours and was made to react at a room temperature. It cools after adding 300ml of ethyl acetate to a reactant, after adjusting to pH7.5 by NaOH 20%, liquids are separated, and it is ethyl acetate to a water layer further. 400ml added and it extracted. The solvent was distilled off under reduced pressure of an ethyl acetate layer. It is water, after adding 120ml to the obtained residue, dissolving an acetonitrile in it under heating and cooling to a room temperature. In addition, 280ml was crystallized and 83.7g (81% of yield) of white crystals of the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal was obtained.

[0026] It is the following, and the capsule I which has the presentation shown in per manufacture 1 capsule [Table 1] of example of reference 3 capsule was made and manufactured. first -- 1 -- 225g and 3 -- 486g and 4 -- 396g and 5 -- 346.5g was often mixed

and it considered as conspergents. 22,700g was put in into centrifugal flow mold coating granulator (the Freund Industrial make, CF-360phi), and the above-mentioned conspergents was coated, carrying out the spray of the 1,116g of the water solutions which dissolved 627.9g. 3 [ furthermore, ] -- 144g and 4 -- 157.5g and 5 -- 157.5g was often mixed, and it considered as control conspergents, it coated following the above-mentioned conspergents, and spherical granulation was obtained. 40 degrees C, the vacuum drying of this spherical granulation was carried out for 16 hours, it carried out screening with the round sieve, and the chief remedy grain (710-1000micro) was obtained. 4,125g of these chief remedy grains was put into the fluidized-bed-granulation drier (Powrex make), and it coated with 4,125g of water solutions containing 7206g, and considered as the bottom credit grain. Furthermore, by the same machine, 8,986g of suspension which contains 8834.4g(2,781. as 30% methacrylic acid copolymer-emulsified liquidg [ 2 ], 9)251.6g, 10 81.4g, and 11 37g in 4,006g of bottom credit grains was coated, and the enteric grain was obtained. 4,506g of this enteric grain, 12 9.6g, and 13 2.56g were used as the mixed grain using the tumbler mixer (made in the Showa chemical machinery machining place), the gelatine capsule No. 4 was filled up with 4,377g of this mixed grain with the encapsulation machine (product made from ZANASHI), and Capsule I was obtained.

[0027] The capsule J which has the presentation shown in per capsule [Table 1] like the example 3 of example of reference 4 reference, and Capsule K were manufactured. It is the drug release of USP about the acid resistance of a capsule and elution nature which were obtained. All were good as a result of evaluating according to the method [USP<724> Drug Release, Delayed-release (Enteric-coated) Articles, Method A, and Apparatus 2 (paddle 50rpm)] of examining 724 publications.

[0028]

[Table 1]

| 組　成（1カプセル当たり） | 5 mg カプセルI | 10 mg カプセルJ | 20 mg カプセルK |
|---|---|---|---|
| 〔主薬粒〕 | (mg) | (mg) | (mg) |
| 1) 化合物A* | 5.0 | 10.0 | 20.0 |
| 2) 白糖・デンプン球状顆粒 | 60.0 | 78.0 | 156.0 |
| 3) 精製白糖 | 14.0 | 16.1 | 32.2 |
| 4) トウモロコシデンプン | 12.3 | 14.6 | 29.2 |
| 5) 低置換度ヒドロキシプロピルセルロース | 11.2 | 14.5 | 29.0 |
| 6) ヒドロキシプロピルセルロース | 0.62 | 0.8 | 1.6 |
| 小計 | 103.12 | 134.0 | 268.0 |
| 〔下掛け粒〕 | | | |
| 主薬粒 | 103.12 | 134.0 | 268.0 |
| 7) ヒドロキシプロピルメチルセルロース2910 | 5.15 | 6.7 | 13.4 |
| 小計 | 108.27 | 140.7 | 281.4 |
| 〔腸溶性粒〕 | | | |
| 下掛け粒 | 108.27 | 140.7 | 281.4 |
| 8) メタアクリル酸コポリマーLD | 22.55 | 29.3 | 58.6 |
| 9) タルク | 6.8 | 8.8 | 17.6 |
| 10) マクロゴール6000 | 2.2 | 2.9 | 5.8 |
| 11) ポリソルベート80 | 1.0 | 1.3 | 2.6 |
| 小計 | 140.82 | 183.0 | 366.0 |
| 〔混合粒〕 | | | |
| 腸溶性粒 | 140.82 | 183.0 | 366.0 |
| 12) タルク | 0.3 | 0.4 | 0.8 |
| 13) 軽質無水ケイ酸 | 0.08 | 0.1 | 0.2 |
| 小計 | 141.2 | 183.5 | 367.0 |
| 〔カプセル剤〕 | | | |
| 混合粒 | 141.2 | 183.5 | 367.0 |
| 14) ゼラチンカプセル4号 | 40.0 | | |
| 15) ゼラチンカプセル3号 | | 49.0 | |
| 16) ゼラチンカプセル1号 | | | 77.0 |
| 計 | 181.2 | 232.5 | 444.0 |

* 化合物A：N－デメチル－N－イソプロピル－8，9－アンヒドロエリスロマイシンA－6，9－ヘミアセタール

[0029]

[Effect of the Invention] according to the manufacture approach of this invention -- efficient -- a short time -- a reaction -- carrying out -- high yield and a high grade -- an erythromycin derivative -- especially -- Since the N-DEMECHIRU-N-isopropyl -8, 9-anhydro erythromycin A-6, 9-hemiacetal, N-DEMECHIRU-N-ethyl -8, 9-anhydro erythromycin A-6, and 9-hemiacetal can be manufactured, the very advantageous approach as a process of using for industrial mass production method can be offered. For example, the inside of the mixed solvent of a N-methyl-2-pyrrolidone or a N-methyl-2-pyrrolidone, and an acetonitrile, N-alkylation reaction, N-alkenyl-ized reaction, or N-alkynyl-ized reaction of N-DEMECHIRU erythromycin derivative, N-DEMECHIRU -8 in the inside of this solvent, 9-anhydro erythromycin -6, N-alkylation reaction of 9-hemiacetal derivative, N-alkenyl-ized reaction or N-alkynyl-ized reaction can complete a reaction efficiently for a short time (about 1 - 8 hours) compared with the conventional approach.

[Translation done.]